



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US98/10940</p> <p>(22) International Filing Date: 29 May 1998 (29.05.98)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>60/048,017</td> <td>29 May 1997 (29.05.97)</td> <td>US</td> </tr> <tr> <td>9714314.3</td> <td>7 July 1997 (07.07.97)</td> <td>GB</td> </tr> <tr> <td>60/066,525</td> <td>25 November 1997 (25.11.97)</td> <td>US</td> </tr> <tr> <td>9800686.9</td> <td>14 January 1998 (14.01.98)</td> <td>GB</td> </tr> </table> <p>(71) Applicant (for all designated States except US): MERCK &amp; CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): DURETTE, Philippe, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HAGMANN, William, K. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MacCOSS, Malcolm</p>		60/048,017	29 May 1997 (29.05.97)	US	9714314.3	7 July 1997 (07.07.97)	GB	60/066,525	25 November 1997 (25.11.97)	US	9800686.9	14 January 1998 (14.01.98)	GB	<p>[GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MILLS, Sander, G. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MUMFORD, Richard, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VAN RIPER, Gail, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SCHMIDT, Jack, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KEVIN, Nancy, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(74) Common Representative: MERCK &amp; CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p><b>Published</b>  <i>With international search report.  Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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<p>(54) Title: HETEROCYCLIC AMIDE COMPOUNDS AS CELL ADHESION INHIBITORS</p> <p>(57) Abstract</p> <p>Compounds of formula (I) are antagonists of VLA-4 and/or <math>\alpha_4\beta_7</math>, and as such are useful in the inhibition or prevention of cell adhesion and cell-adhesion mediated pathologies. These compounds may be formulated into pharmaceutical compositions and are suitable for use in the treatment of asthma, allergies, inflammation, multiple sclerosis, and other inflammatory and autoimmune disorders.</p>														

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**TITLE OF THE INVENTION****HETEROCYCLIC AMIDE COMPOUNDS AS CELL ADHESION INHIBITORS****SUMMARY OF THE INVENTION**

5           The compounds of the present invention are antagonists of the VLA-4 integrin ("very late antigen-4"; CD49d/CD29; or  $\alpha 4\beta 1$ ) and/or the  $\alpha 4\beta 7$  integrin (LPAM-1 and  $\alpha 4\beta p$ ), thereby blocking the binding of VLA-4 to its various ligands, such as VCAM-1 and regions of fibronectin and/or  $\alpha 4\beta 7$  to its various ligands, such as MadCAM-1, VCAM-1 and  
10   fibronectin. Thus, these antagonists are useful in inhibiting cell adhesion processes including cell activation, migration, proliferation and differentiation. These antagonists are useful in the treatment, prevention and suppression of diseases mediated by VLA-4 and/or  $\alpha 4\beta 7$  binding and cell adhesion and activation, such as multiple sclerosis,  
15   asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, septic arthritis, type I diabetes, organ transplantation, restenosis, autologous bone marrow transplantation, inflammatory sequelae of viral infections, myocarditis, inflammatory bowel disease including ulcerative colitis and Crohn's disease, certain  
20   types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, and atherosclerosis.

**BACKGROUND OF THE INVENTION**

25           The present invention relates to heterocyclic amide derivatives which are useful for the inhibition and prevention of leukocyte adhesion and leukocyte adhesion-mediated pathologies. This invention also relates to compositions containing such compounds and methods of treatment using such compounds.

30           Many physiological processes require that cells come into close contact with other cells and/or extracellular matrix. Such adhesion events may be required for cell activation, migration, proliferation and differentiation. Cell-cell and cell-matrix interactions are mediated through several families of cell adhesion molecules

(CAMs) including the selectins, integrins, cadherins and immunoglobulins. CAMs play an essential role in both normal and pathophysiological processes. Therefore, the targetting of specific and relevant CAMs in certain disease conditions without interfering with normal cellular functions is essential for an effective and safe therapeutic agent that inhibits cell-cell and cell-matrix interactions.

The integrin superfamily is made up of structurally and functionally related glycoproteins consisting of  $\alpha$  and  $\beta$  heterodimeric, transmembrane receptor molecules found in various combinations on nearly every mammalian cell type. (for reviews see: E. C. Butcher, Cell, **67**, 1033 (1991); T. A. Springer, Cell, **76**, 301 (1994); D. Cox et al., "The Pharmacology of the Integrins." Medicinal Research Rev. **14**, 195 (1994) and V. W. Engleman et al., "Cell Adhesion Integrins as Pharmaceutical Targets." in Ann. Repts. in Medicinal Chemistry, Vol. 31, J. A. Bristol, Ed.; Acad. Press, NY, 1996, p. 191).

VLA-4 ("very late antigen-4"; CD49d/CD29; or  $\alpha_4\beta_1$ ) is an integrin expressed on all leukocytes, except platelets and mature neutrophils, including dendritic cells and macrophage-like cells and is a key mediator of the cell-cell and cell-matrix interactions of these cell types (see M. E. Hemler, "VLA Proteins in the Integrin Family: Structures, Functions, and Their Role on Leukocytes." Ann. Rev. Immunol. **8**, 365 (1990)). The ligands for VLA-4 include vascular cell adhesion molecule-1 (VCAM-1) and the CS-1 domain of fibronectin (FN). VCAM-1 is a member of the Ig superfamily and is expressed *in vivo* on endothelial cells at sites of inflammation. (See R. Lobb et al. "Vascular Cell Adhesion Molecule 1." in Cellular and Molecular Mechanisms of Inflammation, C. G. Cochrane and M. A. Gimbrone, Eds.; Acad. Press, San Diego, 1993, p. 151.) VCAM-1 is produced by vascular endothelial cells in response to pro-inflammatory cytokines (See A. J. H. Gearing and W. Newman, "Circulating adhesion molecules in disease.", Immunol. Today, **14**, 506 (1993). The CS-1 domain is a 25 amino acid sequence that arises by alternative splicing within a region of fibronectin. (For a review, see R. O. Hynes "Fibronectins.", Springer-

Velag, NY, 1990.) A role for VLA-4/CS-1 interactions in inflammatory conditions has been proposed (see M. J. Elices, "The integrin  $\alpha_4\beta_1$  (VLA-4) as a therapeutic target" in Cell Adhesion and Human Disease, Ciba Found. Symp., John Wiley & Sons, NY, 1995, p. 79).

5                    $\alpha_4\beta_7$  (also referred to as LPAM-1 and  $\alpha_4\beta_p$ ) is an integrin expressed on leukocytes and is a key mediator of leukocyte trafficking and homing in the gastrointestinal tract (see C. M. Parker et al., Proc. Natl. Acad. Sci. USA, **89**, 1924 (1992)). The ligands for  $\alpha_4\beta_7$  include mucosal addressing cell adhesion molecule-1 (MadCAM-1) and, upon  
10 activation of  $\alpha_4\beta_7$ , VCAM-1 and fibronectin (Fn). MadCAM-1 is a member of the Ig superfamily and is expressed in vivo on endothelial cells of gut-associated mucosal tissues of the small and large intestine ("Peyer's Patches") and lactating mammary glands. (See M. J. Briskin et al., Nature, **363**, 461 (1993); A. Hamann et al., J. Immunol., **152**, 3282  
15 (1994)). MadCAM-1 can be induced in vitro by proinflammatory stimuli (See E. E. Sikorski et al. J. Immunol., **151**, 5239 (1993)). MadCAM-1 is selectively expressed at sites of lymphocyte extravasation and specifically binds to the integrin,  $\alpha_4\beta_7$ .

                  Neutralizing anti- $\alpha_4$  antibodies or blocking peptides that  
20 inhibit the interaction between VLA-4 and/or  $\alpha_4\beta_7$  and their ligands have proven efficacious both prophylactically and therapeutically in several animal models of disease, including i) experimental allergic encephalomyelitis, a model of neuronal demyelination resembling multiple sclerosis (for example, see T. Yednock et al., "Prevention of  
25 experimental autoimmune encephalomyelitis by antibodies against  $\alpha_4\beta_1$  integrin." Nature, **356**, **63** (1993) and E. Keszthelyi et al., "Evidence for a prolonged role of  $\alpha_4$  integrin throughout active experimental allergic encephalomyelitis." Neurology, **47**, 1053 (1996)); ii) bronchial  
hyperresponsiveness in sheep and guinea pigs as models for the various  
30 phases of asthma (for example, see W. M. Abraham et al., " $\alpha_4$ -Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep." J. Clin. Invest. **93**, 776 (1993) and A. A. Y. Milne and P. P. Piper, "Role of VLA-4 integrin in leucocyte

recruitment and bronchial hyperresponsiveness in the guinea-pig." Eur. J. Pharmacol., **282**, 243 (1995)); iii) adjuvant-induced arthritis in rats as a model of inflammatory arthritis (see C. Barbadillo et al., "Anti-VLA-4 mAb prevents adjuvant arthritis in Lewis rats." Arthr. Rheuma. (Suppl.), **36** 95 (1993) and D. Seiffge, "Protective effects of monoclonal antibody to VLA-4 on leukocyte adhesion and course of disease in adjuvant arthritis in rats." J. Rheumatol., **23**, 12 (1996)); iv) adoptive autoimmune diabetes in the NOD mouse (see J. L. Baron et al., "The pathogenesis of adoptive murine autoimmune diabetes requires an interaction between  $\alpha_4$ -integrins and vascular cell adhesion molecule-1." J. Clin. Invest., **93**, 1700 (1994), A. Jakubowski et al., "Vascular cell adhesion molecule-Ig fusion protein selectively targets activated  $\alpha_4$ -integrin receptors in vivo: Inhibition of autoimmune diabetes in an adoptive transfer model in nonobese diabetic mice." J. Immunol., **155**, 938 (1995), and X. D. Yang et al., "Involvement of beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MadCAM-1) in the development of diabetes in nonobese diabetic mice", Diabetes, **46**, 1542 (1997)); v) cardiac allograft survival in mice as a model of organ transplantation (see M. Isobe et al., "Effect of anti-VCAM-1 and anti-VLA-4 monoclonal antibodies on cardiac allograft survival and response to soluble antigens in mice.", Transplant. Proc., **26**, 867 (1994) and S. Molossi et al., "Blockade of very late antigen-4 integrin binding to fibronectin with connecting segment-1 peptide reduces accelerated coronary arteriopathy in rabbit cardiac allografts." J. Clin. Invest., **95**, 2601 (1995)); vi) spontaneous chronic colitis in cotton-top tamarins which resembles human ulcerative colitis, a form of inflammatory bowel disease (see D. K. Podolsky et al., "Attenuation of colitis in the Cotton-top tamarin by anti- $\alpha_4$  integrin monoclonal antibody.", J. Clin. Invest., **92**, 372 (1993)); vii) contact hypersensitivity models as a model for skin allergic reactions (see T. A. Ferguson and T. S. Kupper, "Antigen-independent processes in antigen-specific immunity.", J. Immunol., **150**, 1172 (1993) and P. L. Chisholm et al., "Monoclonal antibodies to the integrin  $\alpha_4$  subunit inhibit the murine contact hypersensitivity

response." Eur. J. Immunol., **23**, 682 (1993)); viii) acute neurotoxic nephritis (see M. S. Mulligan et al., "Requirements for leukocyte adhesion molecules in nephrotoxic nephritis.", J. Clin. Invest., **91**, 577 (1993)); ix) tumor metastasis (for examples, see M. Edward, "Integrins and other adhesion molecules involved in melanocytic tumor progression.", Curr. Opin. Oncol., **7**, 185 (1995)); x) experimental autoimmune thyroiditis (see R. W. McMurray et al., "The role of  $\alpha 4$  integrin and intercellular adhesion molecule-1 (ICAM-1) in murine experimental autoimmune thyroiditis." Autoimmunity, **23**, 9 (1996); and xi) ischemic tissue damage following arterial occlusion in rats (see F. Squadrito et al., "Leukocyte integrin very late antigen-4/vascular cell adhesion molecule-1 adhesion pathway in splanchnic artery occlusion shock." Eur. J. Pharmacol., **318**, 153 (1996; xii) inhibition of TH2 T-cell cytokine production including IL-4 and IL-5 by VLA-4 antibodies which would attenuate allergic responses (J. Clinical Investigation **100**, 3083 (1997). The primary mechanism of action of such antibodies appears to be the inhibition of lymphocyte and monocyte interactions with CAMs associated with components of the extracellular matrix, thereby limiting leukocyte migration to extravascular sites of injury or inflammation and/or limiting the priming and/or activation of leukocytes.

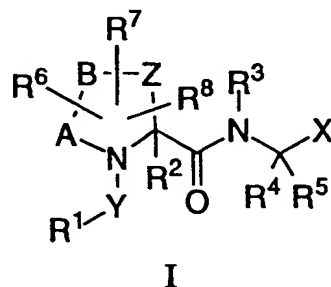
There is additional evidence supporting a possible role for VLA-4 interactions in other diseases, including rheumatoid arthritis; various melanomas, carcinomas, and sarcomas; inflammatory lung disorders; acute respiratory distress syndrome (ARDS); atherosclerotic plaque formation; restenosis; uveitis and circulatory shock (for examples, see A. A. Postigo et al., "The  $\alpha 4\beta 1$ /VCAM-1 adhesion pathway in physiology and disease.", Res. Immunol., **144**, 723 (1994) and J.-X. Gao and A. C. Issekutz, "Expression of VCAM-1 and VLA-4 dependent T-lymphocyte adhesion to dermal fibroblasts stimulated with proinflammatory cytokines." Immunol. **89**, 375 (1996)).

At present, there is a humanized monoclonal antibody (Antegren® Athena Neurosciences/Elan ) against VLA-4 in clinical development for the treatment of "flares" associated with multiple

sclerosis and a humanized monoclonal antibody (ACT-1®/LDP-02 LeukoSite) against  $\alpha_4\beta_7$  in clinical development for the treatment of inflammatory bowel disease. Several peptidyl antagonists of VLA-4 have been described (D. Y. Jackson et al., "Potent  $\alpha_4\beta_1$  peptide antagonists as potential anti-inflammatory agents", J. Med. Chem., **40**, 3359 (1997); H. N. Shroff et al., "Small peptide inhibitors of  $\alpha_4\beta_7$  mediated MadCAM-1 adhesion to lymphocytes", Bioorg. Med. Chem. Lett., **6**, 2495 (1996); US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973). There is one report of nonpeptidyl inhibitors of the ligands for  $\alpha_4$ -integrins (WO96/31206). There still remains a need for low molecular weight, specific inhibitors of VLA-4- and  $\alpha_4\beta_7$ -dependent cell adhesion that have improved pharmacokinetic and pharmacodynamic properties such as oral bioavailability and significant duration of action. Such compounds would prove to be useful for the treatment, prevention or suppression of various pathologies mediated by VLA-4 and  $\alpha_4\beta_7$  binding and cell adhesion and activation.

## DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention provides a method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound Formula I:



or a pharmaceutically acceptable salt thereof wherein:



- R<sup>1</sup> is
- 1) C<sub>1-10</sub>alkyl,
  - 2) C<sub>2-10</sub>alkenyl,
  - 3) C<sub>2-10</sub>alkynyl,
  - 4) Cy,
  - 5) Cy-C<sub>1-10</sub>alkyl,
  - 6) Cy-C<sub>2-10</sub>alkenyl,
  - 7) Cy-C<sub>2-10</sub>alkynyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R<sup>a</sup>; and Cy is optionally substituted with one to four substituents independently selected from R<sup>b</sup>;

- R<sup>2</sup> is
- 1) hydrogen,
  - 2) C<sub>1-10</sub>alkyl,
  - 3) C<sub>2-10</sub>alkenyl,
  - 4) C<sub>2-10</sub>alkynyl,
  - 5) aryl,
  - 6) aryl-C<sub>1-10</sub>alkyl,
  - 7) heteroaryl,
  - 8) heteroaryl-C<sub>1-10</sub>alkyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R<sup>a</sup>; and aryl and heteroaryl optionally substituted with one to four substituents independently selected from R<sup>b</sup>;

- R<sup>3</sup> is
- 1) hydrogen,
  - 2) C<sub>1-10</sub> alkyl,
  - 3) Cy, or
  - 4) Cy-C<sub>1-10</sub> alkyl,

wherein alkyl is optionally substituted with one to four substituents independently selected from R<sup>a</sup>; and Cy is optionally substituted with one to four substituents independently selected from R<sup>b</sup>;

- R<sup>4</sup> is
- 1) hydrogen,

- 5
- 2) C<sub>1-10</sub>alkyl,
  - 3 C<sub>2-10</sub>alkenyl,
  - 4) C<sub>2-10</sub>alkynyl,
  - 5) Cy,
  - 6) Cy-C<sub>1-10</sub>alkyl,
  - 7) Cy-C<sub>2-10</sub>alkenyl,
  - 8) Cy-C<sub>2-10</sub>alkynyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from phenyl and R<sup>x</sup>, and Cy is optionally substituted with one to four substituents independently selected from R<sup>y</sup>; or  
R<sup>3</sup>, R<sup>4</sup> and the atoms to which they are attached together form a mono- or bicyclic ring containing 0-2 additional heteroatoms selected from N, O and S;

15

- R<sup>5</sup> is
- 1) hydrogen,
  - 2) C<sub>1-10</sub>alkyl,
  - 3) C<sub>2-10</sub>alkenyl,
  - 4) C<sub>2-10</sub>alkynyl,
  - 5) aryl,
  - 6) aryl-C<sub>1-10</sub>alkyl,
  - 7) heteroaryl,
  - 8) heteroaryl-C<sub>1-10</sub>alkyl,

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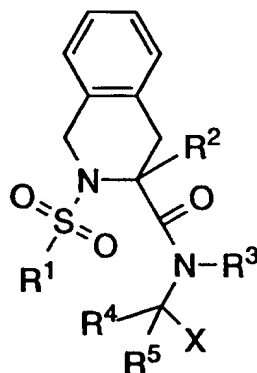
wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents selected from R<sup>x</sup>, and aryl and heteroaryl are optionally substituted with one to four substituents independently selected from R<sup>y</sup>; or

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R<sup>4</sup>, R<sup>5</sup> and the carbon to which they are attached form a 3-7 membered mono- or bicyclic ring containing 0-2 heteroatoms selected from N, O and S;

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8. A compound of Claim 5 wherein X is C(O)OR<sup>d</sup>.
9. A compound of Claim 5 wherein R<sup>1</sup> is C<sub>1-10</sub>alkyl, Cy or Cy-C<sub>1-10</sub>alkyl wherein alkyl is optionally substituted with one to two substituents independently selected from R<sup>a</sup>, and Cy is optionally substituted with one to four substituents independently selected from R<sup>b</sup>.
10. A compound of Claim 5 wherein R<sup>1</sup> is aryl optionally substituted with one to four substituents selected from R<sup>b</sup>.
11. A compound of Claim 5 wherein R<sup>5</sup> is H and R<sup>4</sup> is C<sub>1-10</sub> alkyl or Cy-C<sub>1-10</sub>alkyl, wherein alkyl is optionally substituted with one to four substituents selected from phenyl and R<sup>x</sup>, and Cy is optionally substituted with one to four substituents independently selected from R<sup>y</sup>; or R<sup>4</sup>, R<sup>5</sup> and the carbon to which they are attached together form a 3-7 membered mono- or bicyclic carbon only ring.
12. A compound of Claim 11 wherein R<sup>4</sup> is phenyl-C<sub>1-3</sub> alkyl, wherein phenyl is optionally substituted with one or two groups selected from R<sup>y</sup>.
13. A compound of Claim 5 having the formula Ib:

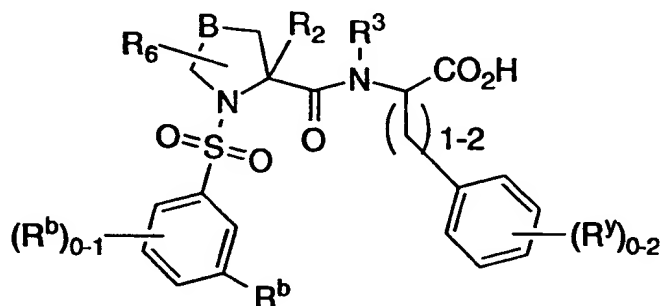


wherein  $R^2$  is H or C<sub>1-6</sub> alkyl, and  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  and X are as defined in Claim 5.

- 5                    14. A compound of Claim 13 wherein X is CO<sub>2</sub>H;  $R^1$  is aryl optionally substituted with one to four substituents selected from  $R^b$ ;  $R^2$  is H;  $R^3$  H or C<sub>1-3</sub> alkyl;  $R^4$  is phenyl-C<sub>1-3</sub>alkyl, wherein phenyl is optionally substituted with one or two groups selected from  $R^y$ ; and  $R^5$  is H.

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15. A compound of Claim 5 having the formula Ic:



15

Ic

wherein  $R^2$  is H or C<sub>1-3</sub> alkyl;  $R^6$  is H, C<sub>1-6</sub> alkyl, aryl, OR<sup>d</sup>, SR<sup>d</sup>, NR<sup>d</sup>Re, or NR<sup>d</sup>C(O)R<sup>e</sup>; B is S, C=C, C or C-C;  $R^3$  is H or C<sub>1-6</sub>alkyl,  $R^b$  and  $R^y$  are as defined in Claim 5.

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16. A compound of Claim 15 wherein B is C and  $R^b$  is halogen, C<sub>1-10</sub>alkoxy, cyano, or trifluoromethyl.

17. A compound selected from the group consisting of:  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-leucine;

N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-arginine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-glutamic acid;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-glycine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-(1-naphthyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)- $\alpha$ -t-butylglycine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(2-thienyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-cyclohexylalanine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(2-naphthyl)alanine;  
N-(3,3-diphenylpropanoyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2,4-dinitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3,3-diphenylalanine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-proline;  
N-dansyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2-naphthalenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-methoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;

N-(4-phenylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3,4-dimethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-cysteine;  
N-(4-t-butylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2,5-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2-mesitylenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(p-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-chlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(N'-acetylsulfanilyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-fluorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(1-naphthalenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(benzylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-phenylalanine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-glutamine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-(4-nitrophenyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-asparagine;

N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-methionine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-homophenylalanine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(D)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-(4-fluorophenyl)alanine;  
N-(3-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-trifluoromethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-n-propylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-isopropylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2,6-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-ethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2,4-difluorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2-cyanobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-tert-amylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-chloro-3-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3-cyanobenzoyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3,5-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;

N-(3,4-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2-trifluoromethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2,3-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2,4-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2,5-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-serine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-isoleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-tryptophan;  
N-(2,1,3-benzothiadiazole-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-tryptophan;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(3-pyridyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-3-(2-naphthyl)alanine, ethyl ester;  
N-acetyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(R)-carbonyl-(D)-norleucine;  
N-propionyl-(L)-prolyl-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(4-cyanobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(benzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;



N-(3-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3-trifluoromethylbenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(2-thienylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-N-methylleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-citrulline;  
N-(4-iodobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3(S)-carbonyl-(L)-norleucine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-(3-iodo)tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(3-pyridyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-glutamic acid;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-arginine;  
N-(N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl)-1-amino-cyclopentane-1-carboxylic acid;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(3,4-dichlorophenyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine, ethyl ester;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-bromophenyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-nitrophenyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-thiazolyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-chlorophenyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-chlorophenyl)alanine;

N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(4-cyanophenyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, O-sulfate;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3,5-diiodotyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-aspartic acid;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tryptophan;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-methionine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(3,5-di(trifluoromethyl)benzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-thiaprolyl-(L)-norleucine;  
N-[4-(N'-2-toluyllureido)phenylacetyl]-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-norleucine, ethyl ester;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-homophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-(3-iodo)tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine;  
N-[4-(N'-2-toluyllureido)phenylacetyl]-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine;  
N-[3,5-di(trifluoromethyl)benzenesulfonyl]-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine, ethyl ester;

N-(3,4-dimethoxybenzenesulfonyl)-(L)-octahydroisoquinoline-3-carbonyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-azetidine-2-carbonyl-(L)-norleucine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(S)-hydroxypropyl-(L)-3-(2-naphthyl)alanine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-4(S)-hydroxypropyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-norleucine;  
N-(3-bis(N,N-benzenesulfonyl)aminobenzenesulfonyl)-(L)-propyl-(L)-norleucine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-propyl-(L)-3-(4-pyridyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminopropyl-(L)-3-(2-naphthyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-4-fluorophenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-propyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-iodotyrosine;  
N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3-(2-naphthyl)alanine;  
N-(3-fluorobenzenesulfonyl)-(L)-pipecolyl-(L)-3-(2-naphthyl)alanine;  
N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine;  
N-(3-fluorobenzenesulfonyl)-(L)-propyl-(L)-4-fluorophenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-4-fluorophenylalanine;  
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-4-fluorophenylalanine;

N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-pipecolyl-(L)-4-fluorophenylalanine;  
N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-propyl-(L)-tyrosine;  
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine;  
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine;  
N-(3-fluorobenzenesulfonyl)-(L)-pipecolyl-(L)-4-fluorophenylalanine;  
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine, O-tert-butyl ether;  
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxypropyl-(L)-tyrosine, O-tert-butyl ether;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine  
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(S)-methyl-propyl-(L)-4-fluorophenylalanine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine;  
N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine, O-tert-butyl ether;  
N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydropropyl-(L)-tyrosine, O-tert-butyl ether;  
N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-propyl-(L)-4-fluorophenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-propyl-(L)-tyrosine;  
N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-propyl-(L)-tyrosine, O-tert-butyl ether;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-propyl-(L)-tyrosine;  
N-(3-fluorobenzenesulfonyl)-(L)-propyl-(L)-3-iodotyrosine;  
N-(3-chlorobenzenesulfonyl)-(L)-propyl-(L)-3-iodotyrosine;

N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-3-phenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;  
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-3-(4-pyridyl)alanine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-thiaprolyl-(L)-3-(4-pyridyl)alanine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-phenylalanine;  
N-(3-trifluoromethylbenzenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(3-trifluoromethylbenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine;  
N-(3-fluorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine, O-phosphoric acid;  
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-tyrosine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine;  
N-(N<sub>1</sub>-methyl-4-imidazolesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(D)-prolyl-(D)-4-fluorophenylalanine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-3-(4-pyridyl)alanine;  
N-(5-(5-trifluoromethyl-2-pyridylsulfonyl)-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;

N-(5-(N-(4-chlorobenzoyl)aminomethyl)-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(5-(3-(1-methyl-5-trifluoromethyl-pyrazoyl))-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(3-fluorobenzenesulfonyl)-2(S)-methylprolyl-(L)-O-tert-butyl-tyrosine;  
N-(3-fluorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(S)-aminoprolyl-(L)-4-fluorophenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-4-fluorophenylalanine;  
N-(4-bromo-5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-3,5-diiodotyrosine;  
N-(5-benzoylaminomethyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(5-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(3-bromo-5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-3,4-dehydroprolyl-(L)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-homophenylalanine;

N-(4-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(5-benzoylaminomethyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(trans-2-phenyl-ethylene-sulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(5-benzenesulfonyl-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(3-fluorobenzenesulfonyl)-(L)-thiaprolyl-(L)-O-tert-butyl-tyrosine;  
N-(benzylsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-cysteine, amide;  
N-(1-methyl-4-imidazolylsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(4-(N-(4-dimethylaminophenyl)diazo)-benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(5-(4-trifluoromethylbenzenesulfonyl)-2-thiophenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(3-bromobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(4-methylsulfonyl-benzenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(4-methoxybenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-3-fluorophenylalanine;  
N-(5-chloro-2-thiophenesulfonyl)-(L)-prolyl-(L)-4-fluorophenylalanine;  
N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-O-tert-butyl-tyrosine;  
N-(1(R)-(+)-10-camphorsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(1(S)-(+)-10-camphorsulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;

N-(3,4-methylenedioxy-phenylacetyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-hydroxyprolyl-(L)-tyrosine-O-sulfate;  
N-(3-chlorobenzenesulfonyl)-(L)-thiaprolyl-(L)-tyrosine-O-sulfate;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-cysteine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-N-methyl-isoleucine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine;  
N-(3-chlorobenzenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine;  
N-(3-cyanobenzenesulfonyl)-(L)-prolyl-(L)-tyrosine;  
N-benzenesulfonyl-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(4-methylsulfonylbenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-O-tert-butyl-tyrosine;  
N-(4,5-dichloro-2-thiophenesulfonyl)-(L)-4(R)-aminoprolyl-(L)-4-fluorophenylalanine;  
N-(9-fluorenylmethyloxycarbonyl)-(L)-prolyl-(L)-phenylalanine;  
N-(benzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;  
N-(n-octyl-1-sulfonyl)-(L)-prolyl-(L)-phenylalanine;  
N-(3-fluorobenzenesulfonyl)-(L)-5(R)-phenyl-prolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-phenyl-prolyl-(L)-4-iodophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-1,3-dihydro isoindolyl-1-carbonyl-(L)-4-fluorophenylalanine;  
N-(4-(fluorescien-4-carboxylamino)benzene sulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;



N-(3-ethoxycarbonyl-benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(4-iodobenzenesulfonyl)-(L)-prolyl-(L)-4-benzoyl-phenylalanine;  
N-(3-(4-benzophenonyl-carbonylamino)-benzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(3-(6-(biotinylamino)-n-hexanoyl)-aminobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-[3.1.0]-3-azabicyclohexane-2-carbonyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-[4-(N'-2-toluyllureido)phenylacetyl-(L)-prolyl-(L)-norleucine;  
N-(3,4-dimethoxybenzoyl)-(L)-prolyl-(L)-norleucine;  
N-(3,4-dimethoxybenzenesulfonyl)-(L)-pipecolyl-(L)-tryptophan;  
N-(4-nitrobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-[3,5-di(trifluoromethyl)benzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(3-trifluoromethylbenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-[4-(benzoylamino)benzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(4-methoxy-3,5-dinitrobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(3-trifluoromethylbenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(3-nitrobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(3-cyanobenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-tryptophan;  
N-(3-methylbenzenesulfonyl)-(L)-prolyl-(L)-norleucine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(S)-methyl-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(3-chlorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-phenylacetyl-(L)-prolyl-(L)-3-(2-naphthyl)alanine;

N-(3-phenylpropionyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(phenylaminocarbonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2-methyl-prolyl-(L)-3-(2-naphthyl)-alanine;  
N-(benzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(4-N'-phenylureidobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(3-fluorobenzenesulfonyl)-(L)-5,5-dimethyl-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(4-N'-(2-toluy)ureidobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-iodophenylalanine;  
N-(4-N'-benzylureidobenzenesulfonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(phenyloxalyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(benzylaminocarbonyl)-(L)-prolyl-(L)-3-(2-naphthyl)alanine;  
N-(3-fluorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalaninamide-N-methylsulfonamide;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-iodophenylalanine;  
N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-5-methylprolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-3-phenylazetidiny carbonyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-allylprolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-phenylalanine;

N-(3-trifluoromethylbenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-nitro-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methyl-prolyl-(L)-4-fluorophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-cyanophenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(aminocarbonyl)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methyl-prolyl-(L)-4-(N-t-butoxycarbonylaminomethyl)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-3(R)-methyl-prolyl-(L)-4-(aminomethyl)-phenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-acetaminophenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(2-toluy)ureido)phenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(4'-fluorophenylsulfonyl)ureido)phenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(ethoxycarbonyl)aminophenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-(N'-(2-toluy)ureido)phenylacetyl)aminophenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-fluorophenylsulfonyl)aminophenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(phenylacetyl)aminophenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-fluorobenzoyl)aminophenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(isobutyloxycarbonyl)aminophenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-methylsulfonylamino-phenylalanine;

N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(4-fluorophenyl)ureido)phenylalanine;  
N-(3-trifluoromethylbenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N-(1,1-dioxo-1,2-isothiazolidinyl)-phenylalanine;  
N-(3-trifluoromethylphenylsulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(N'-(4-(2-oxo-1-pyrrolidinyl)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4'-fluorobenzoyl)phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-methoxybenzoyl)phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(4'-fluorobenzoyl)phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-fluorobenzyl)phenyl alanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-methoxybenzyl)phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-nitrophenoxy)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-nitrophenoxy)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(2-nitrophenoxy)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-aminophenoxy)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(2-acetylaminophenoxy)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-4-(4-acetylaminophenoxy)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methylprolyl-(L)-4-(2-acetylaminophenoxy)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(2-cyanophenoxy)-phenylalanine;

N-(3,5-dichlorobenzenesulfonyl)-2-(S)-methyl-(L)-prolyl-4-(4-cyanophenoxy)-phenylalanine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-tert-butyl-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-methyl-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-benzyl-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-n-butyl-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-cyanomethyl-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-methoxyethyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine;  
N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(2-methoxyethyl)-tyrosine;  
N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine;  
N-(benzenesulfonyl)-(L)-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(tert-butyl acetate)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(4-morpholinylcarbonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(1-(2-propanonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(tert-butyl acetate)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(2-ethoxyethyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(acetic acid)-tyrosine, methyl ester;

N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(acetic acid)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-(2-propanonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(1-pyrrolidinylcarbonyl)-tyrosine, methyl ester;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(4-morpholinyl-carbonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(2-pyrrolylcarbonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N-phenyl-N-methylaminocarbonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N,N-diethyl-aminocarbonyl)-tyrosine;  
N-(3-chlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(4-morpholinyl-carbonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-O-(N,N-diisopropyl-aminocarbonyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(benzoyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(cyclopentanoyl)-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-prolyl-(L)-O-(5-tetrazolyl)methyl-tyrosine;  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-N<sup>c</sup>-benzyl-histidine;  
N-benzenesulfonyl-(L)-prolyl-2-amino-2-norbornanecarboxylic acid;  
N-benzenesulfonyl-(L)-prolyl-3(R)-methyl-phenylalanine;  
N-benzenesulfonyl-(L)-prolyl-(L)-2,3-methano-phenylalanine;  
N-benzenesulfonyl-(L)-prolyl-(D)-2,3-methano-phenylalanine; and  
N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(5-((1H,3H)-1,3-dimethylpyrimidine-2,4-dione))-phenylalanine.

18. A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 5.

5

19. A method for the treatment of asthma, allergic rhinitis, multiple sclerosis, atherosclerosis, inflammatory bowel disease or inflammation in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 5.

10

20. A pharmaceutical composition which comprises a compound of Claim 5 and a pharmaceutically acceptable carrier thereof.